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(71) Applicant *(for all designated States except US)*: **BAYER HEALTHCARE AG** [DE/DE]; 51368 Leverkusen (DE).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **YALKINOGLU, Özkan** [DE/DE]; Rückertweg 26, 42115 Wuppertal (DE); **KÖNIG, Gerhard** [DE/US]; 10 Linden St., Arlington, MA 02476 (US). **HOCHSTRASSER, Denis, Francois** [CH/CH]; Chemin de la Savonnière, CH-1245 Collonge-Bellerive (CH). **SANCHEZ, Jean-Charles** [CH/CH]; 42 chemin Frank-Thomas, CH-1208 Geneva (CH). **CARRETTE, Odile** [FR/FR]; 71, rue de la Duquenière, F-59100 Roubaix (FR).

(74) Common Representative: **BAYER HEALTHCARE AG**; Law and Patents, Patents and Licensing, 51368 Leverkusen (DE).

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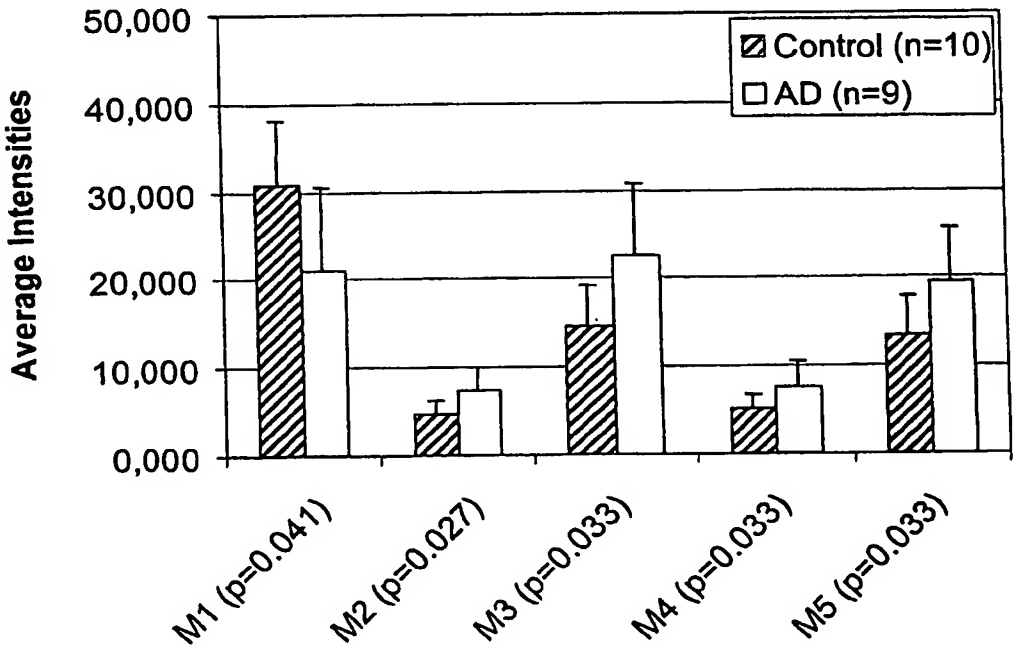
[Continued on next page]

(54) Title: POLYPEPTIDE BIOMARKERS FOR DIAGNOSING ALZHEIMER'S DISEASE



(57) Abstract: A method for assessing the state of Alzheimer's disease in patients is disclosed. A method for monitoring the progression of Alzheimer's disease in patients is also disclosed. The method applies detection of specific markers in body fluids (e.g. CSF), using mass spectrometric analysis (SELDI-TOF MS). The specific markers are: human cystatin C, human beta-2-microglobulin, human myoglobin neurosecretory protein VGF or fragments of these proteins.

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ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)*

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/08879

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N33/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data, PAJ, BIOSIS, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00/25138 A (NITSCH ROGER ;GROWDON JOHN (US)) 4 May 2000 (2000-05-04) the whole document example 1	4
Y		3-8,10

X	WEI, LIHONG ET AL: "Cystatin C: Icelandic-like mutation in an animal model of cerebrovascular.beta.-amyloidosis" STROKE (DALLAS) (1996), 27(11), 2080-2085, XP000998699 the whole document figure 2	3,4
Y		3-8,10

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 December 2003	04 05 2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Tuynman, A

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Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/08879

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	UTAL A ET AL: "Preliminary expression analysis in Alzheimer's disease using SELDI protein chips." SOCIETY FOR NEUROSCIENCE ABSTRACTS, vol. 26, no. 1-2, 2000, pages Abstract No.-83.7, XP000989844 30th Annual Meeting of the Society of Neuroscience;New Orleans, LA, USA; November 04-09, 2000 ISSN: 0190-5295 abstract	3,4,6
A	WO 01/63294 A (OXFORD GLYCOSCIENCES UK LTD ;HERATH HERATH MUDIYANSELAGE AT (GB);) 30 August 2001 (2001-08-30) the whole document	3,4
P,X	DATABASE BIOSIS [Online] BIOSCIENCES INFORMATION SERVICE, PHILADELPHIA, PA, US; March 2003 (2003-03), CARRETTE ODILE ET AL: "A new sensitive and highly specific test for the diagnosis of Alzheimer disease using the ProteinChip(R) technology." XP002265308 Database accession no. PREV200300358956 abstract & FASEB JOURNAL, vol. 17, no. 4-5, March 2003 (2003-03), page Abstract No. 80.3, FASEB Meeting on Experimental Biology: Translating the Genome;San Diego, CA, USA; April 11-15, 2003 ISSN: 0892-6638 (ISSN print)	3-8,10

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/08879

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☒ Claims Nos.: 1,2,9
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
3-8, 10 (partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 1,2,9

Present claims 1,2 and 9 relate to an extremely large number of possible compounds (polypeptides) in methods and kits for the detction of the state of Alzheimer disease, for which a lack of clarity (and conciseness) and support within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.
Polypeptide markers that are only characterized by their molecular weight, comprise an enormous amount of polypeptides that have no relation to Alzheimer's disease at all, which can therfore not be distinguishable for Alzheimer's disease. Therefore the claims are not supported (Article 6 PCT) and do not enable (Article 5 PCT) the person skilled in the art over the whole breadth of the claim.
Consequently, the search has been not carried out for these claims.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 3-8,10 (partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is human cystatin C or a fragment thereof, comprising the sequence SEQ ID NO: 7.

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2. claims: 3-8,10 (partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is human cystatin C or a fragment thereof, comprising the sequence SEQ ID NO: 8.

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3. claims: 3-8,10 (partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is human cystatin C or a fragment thereof, comprising the sequence SEQ ID NO: 9.

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4. claims: 3-8,10 (partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is human cystatin C or a fragment thereof, comprising the sequence SEQ ID NO: 10.

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5. claims: 3-8,10 (partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is human cystatin C or a fragment thereof, comprising the sequence SEQ ID NO: 11.

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6. claims: 3-8,10 (partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is human cystatin C or a fragment thereof, comprising the sequence SEQ ID NO: 12.

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7. claims: 3-8,10 (partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is human cystatin C or a fragment thereof, comprising the sequence SEQ ID NO: 13.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

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8. claims: 3-8,10 (partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is human cystatin C or a fragment thereof, comprising the sequence SEQ ID NO: 14.

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9. claims: 3-8,10 (partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is human cystatin C or a fragment thereof, comprising the sequence SEQ ID NO: 15.

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10. claims: 3-8,10 (partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is human cystatin C or a fragment thereof, comprising the sequence SEQ ID NO: 16.

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11. claims: 3-8,10 (partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is human beta-2-microglobulin or fragments thereof.

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12. claims: 3-8,10 (partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is human myoglobin or a fragment thereof.

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13. claims: 3-8,10 (partially)

Methods and kits for assessing the state of Alzheimer's disease in which the polypeptide marker is neurosecretory protein VGF or a fragment thereof.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/08879

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